PATENT
Attorney Docket No. 175931
DHHS Ref. No. E-167-97/2

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

Mitchell et al.

Group Art Unit: 1614

Application No. 09/424,519

Examiner: B. Y. S. Kwon

Filed: March 3, 2000

For: THE USE OF A NITROXIDE OR A PRODRUG THEREOF IN THE PROPHYLACTIC AND THERAPEUTIC TREATMENT OF CANCER

**DECLARATION UNDER 37 C.F.R. § 1.131 OF JAMES B. MITCHELL**

Commisioner for Patents
Washington, D.C. 20231

I, James B. Mitchell, hereby declare that:

1. I am a co-inventor identified on all of the subject patent application, the parent International Patent Application No. PCT/US98/10685, which was filed May 27, 1998, the parent U.S. Provisional Patent Application No. 60/047,724, which was filed May 27, 1997.

2. Attached hereto as Exhibit 1 are copies of nine pages from an animal lab notebook dated from prior to May 6, 1997, through July 22, 1997. Pages 1 and 2 demonstrate that the p53 knock-out mice (KO1) that were used in the experiments supporting the present inventive methods were received prior to May 6, 1997 and were placed on Tempol or sugar water shortly thereafter. Page 3 describes background and phenotypic information of the KO1 mice. Page 4 demonstrates a summary of information relating to the experiments performed on the KO1 mice. As evident from page 4, both male (M) and female (F) KO1 mice were either administered Tempol (T) or sugar water (C) on the indicated date of treatment (Tx Date) and sacrificed on the indicated date (Sac Date). The autopsy notes of these mice are found on pages 5-7 of Exhibit 1 (dated from prior to May 6, 1997, through July 14, 1997). Page 8 of Exhibit 1 (dated July 22, 1997) demonstrates a pathology/histotechnology laboratory pathology report of the KO1 mice.

Finally, page 9 demonstrates a graph of the results of the experiments performed on the KO1 mice. As evident from page 9, the percent survival is increased for mice that were treated with Tempol.

3. I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

James B. Mitchell

James B. Mitchell, Ph.D.

Date: 1/16/03

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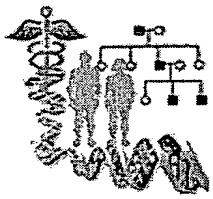

# Genetics Home Reference

*Your Guide to Understanding Genetic Conditions*

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## Li-Fraumeni syndrome

Print version

Li-Fraumeni syndrome

- Related Gene(s)
- Quick links to this topic

NIH Publications
National Institutes of Health

MedlinePlus
Health Information

Genes and Disease
Genetic disorder summaries

Educational resources
Information pages

Patient support
For patients and families

Gene Reviews
Clinical summary

Gene Tests
DNA test labs

ClinicalTrials.gov
Research studies

PubMed
Recent literature

OMIM
Genetic disorder catalog

- References

On this page:


- What is Li-Fraumeni syndrome?
- How common is Li-Fraumeni syndrome?
- What genes are related to Li-Fraumeni syndrome?
- How do people inherit Li-Fraumeni syndrome?
- Where can I find additional information about Li-Fraumeni syndrome?
- What other names do people use for Li-Fraumeni syndrome?
- What if I still have specific questions about Li-Fraumeni syndrome?
- What glossary definitions help with understanding Li-Fraumeni syndrome?


### What is Li-Fraumeni syndrome?

Li-Fraumeni syndrome is a rare inherited disorder that greatly increases the risk of developing several types of cancer, particularly in children and young adults.

The cancers associated with Li-Fraumeni syndrome include osteosarcoma (a form of bone cancer), soft tissue sarcoma (cancer that occurs in soft tissues such as muscle), breast cancer, brain tumors, adrenocortical carcinoma (cancer of the adrenal gland, a small hormone-producing gland on top of each kidney), and leukemia (a cancer of blood-forming tissue). Other types of cancer also occur more frequently in people with Li-Fraumeni syndrome.

### How common is Li-Fraumeni syndrome?

Li-Fraumeni syndrome is rare. Fewer than 400 families worldwide have been diagnosed with the condition.

### What genes are related to Li-Fraumeni syndrome?

The CHEK2 and TP53 genes are associated with Li-Fraumeni syndrome.

More than half of all families with this condition have inherited mutations in the TP53 gene. TP53 is a tumor suppressor gene, which means that it normally helps control the growth and division of cells. Mutations in TP53 can allow cells to divide in an uncontrolled way and form tumors. Other genetic and environmental factors are also likely to affect the risk of cancer in people with TP53 mutations.

A few families with cancers characteristic of Li-Fraumeni syndrome do not have TP53 mutations, but have mutations in the CHEK2 gene. Like the TP53 gene, CHEK2 is a tumor suppressor gene. Researchers are uncertain whether CHEK2 mutations actually cause Li-Fraumeni syndrome or are merely associated with an increased risk of certain cancers (including breast cancer).

## How do people inherit Li-Fraumeni syndrome?

Li-Fraumeni syndrome is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to increase the risk of developing cancer. In most cases, an affected person has one parent with the condition.

## Where can I find additional information about Li-Fraumeni syndrome?

You may find the following resources about Li-Fraumeni syndrome helpful. These materials are written for the general public.

- NIH Publications - National Institutes of Health (2 links)
- MedlinePlus - Health Information (2 links)
- Genes and Disease - Genetic disorder summaries
- Educational resources - Information pages
  Orphanet
- Patient support - For patients and families (4 links)

You may also be interested in these resources, which are designed for healthcare professionals and researchers.

- Gene Reviews - Clinical summary
- Gene Tests - DNA tests ordered by healthcare professionals
- ClinicalTrials.gov - Linking patients to medical research
- PubMed - Recent literature
- OMIM - Genetic disorder catalog (2 links)

## What other names do people use for Li-Fraumeni syndrome?

- LFS
- Sarcoma, breast, leukemia, and adrenal gland (SBLA) syndrome
- Sarcoma family syndrome of Li and Fraumeni
- SBLA syndrome

See How are genetic conditions and genes named? in the Handbook.

## What if I still have specific questions about Li-Fraumeni syndrome?

- See How can I find a genetics professional in my area? in the Handbook.
- Ask the Genetic and Rare Diseases Information Center ⇨.
- Submit your question to Ask the Geneticist ⇨.

## Where can I find general information about genetic conditions?

The Handbook provides basic information about genetics in clear language.

- What does it mean if a disorder seems to run in my family?
- What are the different ways in which a genetic condition can be inherited?
- If a genetic disorder runs in my family, what are the chances that my children will have the condition?
- Why are some genetic conditions more common in particular ethnic groups?

These links provide additional genetics resources that may be useful.

- Genetics and health
- Resources for Patients and Families
- Resources for Health Professionals

## What glossary definitions help with understanding Li-Fraumeni syndrome?

adrenal glands ; autosomal ; autosomal dominant ; cancer ; carcinoma ; cell ; gene ; hormone ; kidney ; leukemia ; mutation ; osteosarcoma ; sarcoma ; soft tissue ; syndrome ; tissue ; tumor ; tumor suppressor gene

You may find definitions for these and many other terms in the Genetics Home Reference Glossary.

References (7 links)

The resources on this site should not be used as a substitute for professional medical care or advice. Users seeking information about a personal genetic disease, syndrome, or condition should consult with a qualified healthcare professional. See How can I find a genetics professional in my area? in the Handbook.

*Last Comprehensive Review: October 2005*
*Published: March 17, 2006*

1: Semin Cancer Biol. 1996 Oct;7(5):269-78.





# The p53-deficient mouse: a model for basic and applied cancer studies.

**Donehower LA**.

Division of Molecular Virology, Baylor College of Medicine, Houston, TX 77030, USA.

Inactivation of the p53 gene in the germline of mice by gene targeting has provided researchers with a model similar in many respects to the analogous human inherited cancer predisposition Li-Fraumeni syndrome. The viability of p53 null mice has allowed unexpected opportunities to study the role of p53 in many different in-vivo and in-vitro contexts. Null (p53-/-) mice have an average time to tumor development of 4.5 months, while half of the heterozygous (p53+/-) mice develop tumors by 18 months. The p53-deficient mice have been particularly valuable in examining the effects of p53 loss on tumor progression. In addition, the mice hold significant promise as tools to assess carcinogens, teratogens, chemopreventative agents, and cancer therapeutic regimens.

Publication Types:
- Review

PMID: 9110404 [PubMed - indexed for MEDLINE]

1: Science. 1991 Jul 5;253(5015):49-53. Related Articles, Links

# p53 mutations in human cancers.

Hollstein M, Sidransky D, Vogelstein B, Harris CC.

Laboratory of Human Carcinogenesis, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.

Mutations in the evolutionarily conserved codons of the p53 tumor suppressor gene are common in diverse types of human cancer. The p53 mutational spectrum differs among cancers of the colon, lung, esophagus, breast, liver, brain, reticuloendothelial tissues, and hemopoietic tissues. Analysis of these mutations can provide clues to the etiology of these diverse tumors and to the function of specific regions of p53. Transitions predominate in colon, brain, and lymphoid malignancies, whereas G:C to T:A transversions are the most frequent substitutions observed in cancers of the lung and liver. Mutations at A:T base pairs are seen more frequently in esophageal carcinomas than in other solid tumors. Most transitions in colorectal carcinomas, brain tumors, leukemias, and lymphomas are at CpG dinucleotide mutational hot spots. G to T transversions in lung, breast, and esophageal carcinomas are dispersed among numerous codons. In liver tumors in persons from geographic areas in which both aflatoxin B1 and hepatitis B virus are cancer risk factors, most mutations are at one nucleotide pair of codon 249. These differences may reflect the etiological contributions of both exogenous and endogenous factors to human carcinogenesis.

Publication Types:
- Review

PMID: 1905840 [PubMed - indexed for MEDLINE]

**Science for the Brain**
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Studies with patients
Research literature
Press releases

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# NINDS Ataxia Telangiectasia Information Page

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**Table of Contents (click to jump to sections)**

What is Ataxia Telangiectasia?
Is there any treatment?
What is the prognosis?
What research is being done?

Organizations
Related NINDS Publications and Information

**What is Ataxia Telangiectasia?**
Ataxia telangiectasia (A-T) is a rare, progressive, neurodegenerative childhood disease that affects the brain and other body systems. The first signs of the disease, which include delayed development of motor skills, poor balance, and slurred speech, usually occur during the first decade of life. Telangiectasias (tiny, red "spider" veins), which appear in the corners of the eyes or on the surface of the ears and cheeks, are characteristic of the disease, but are not always present and generally do not appear in the first years of life. About 20% of those with A-T develop cancer, most frequently acute lymphocytic leukemia or lymphoma. Many individuals with A-T have a weakened immune system, making them susceptible to recurrent respiratory infections. Other features of the disease may include mild diabetes mellitus, premature graying of the hair, difficulty swallowing, and delayed physical and sexual development. Children with A-T usually have normal or above normal intelligence.

**Is there any treatment?**
There is no cure for A-T and, currently, no way to slow the progression of the disease. Treatment is symptomatic and supportive. Physical and occupational therapy may help maintain flexibility. Speech therapy may also be needed. Gamma-globulin injections may be given to help supplement a weakened immune system. High-dose vitamin regimens may also be used.

**What is the prognosis?**
The prognosis for individuals with A-T is poor. Those with the disease usually die in their teens or early 20s.

**What research is being done?**
NINDS-supported researchers recently discovered the A-T gene, which could lead to more accurate diagnosis of the disease and the development of effective treatments. In addition to supporting basic research on A-T, NINDS funds research aimed at therapeutics development, including development of animal models, gene and stem cell-based therapies, and high-throughput drug screens.

Select this link to view a list of studies currently seeking patients.

## Organizations

**Ataxia Telangiectasia (A-T) Children's Project**
668 South Military Trail
Deerfield Beach, FL 33442-3023
Info@atcp.org
http://www.atcp.org
Tel: 954-481-6611 800-5-HELP-A-T (543-5728)
Fax: 954-725-1153

**Ataxia Telangiectasia (A-T) Medical Research Foundation**
5241 Round Meadow Road
Hidden Hills, CA 91302
becca4435@aol.com
http://www.gspartners.com/at/
Tel: 818-704-8146
Fax: 818-704-8310

**National Ataxia Foundation (NAF)**
2600 Fernbrook Lane N.
Suite 119
Minneapolis, MN 55447-4752
naf@ataxia.org
http://www.ataxia.org
Tel: 763-553-0020
Fax: 763-553-0167

**Ataxia Telangiectasia (A-T) Ease Foundation**
532 LaGuardia Place
Suite 404
New York, NY 10012
GoFordham@aol.com
Tel: 212-529-0622
Fax: 212-505-8031

**National Organization for Rare Disorders (NORD)**
P.O. Box 1968
(55 Kenosia Avenue)
Danbury, CT 06813-1968
orphan@rarediseases.org
http://www.rarediseases.org
Tel: 203-744-0100 Voice Mail 800-999-NORD (6673)
Fax: 203-798-2291

**National Cancer Institute (NCI)**
National Institutes of Health, DHHS
6116 Executive Boulevard, Ste. 3036A, MSC 8322
Bethesda, MD 20892-8322
cancer.gov_staff@mail.nih.gov
http://cancer.gov
Tel: 800-4-CANCER (422-6237) 800-332-8615 (TTY)

## Related NINDS Publications and Information

- NINDS Ataxias and Cerebellar/Spinocerebellar Degeneration Information Page
  Ataxias and Cerebellar/Spinocerebellar Degeneration information sheet compiled by the National Institute of Neurological Disorders and Stroke (NINDS).
- Drug Screening for Ataxia-Telangiectasia
- The Role of DNA Damage Response Defects in Neurogenetic Diseases
  The Role of DNA Damage Response Defects in Neurogenetic Diseases

Prepared by:
Office of Communications and Public Liaison
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, MD 20892

through consultation with a physician who has examined that patient or is familiar with that patient's medical history.



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Last updated February 27, 2006

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1: Cancer Genet Cytogenet. 1993 Apr;66(2):128-9. Related Articles, Links

# Lack of mutations in the P53 gene exons 5 to 8 in ataxia-telangiectasia.

Jonveaux P, Berger R.

INSERM U 301, IGM, Paris, France.

Alterations of the TP53 tumor suppressor gene are present in various human malignancies and in the dominantly inherited Li-Fraumeni syndrome. Recently, a cell cycle checkpoint pathway involving p53 and GADD45 has been identified as defective in ataxia-telangiectasia. Using single strand conformation polymorphism analysis of PCR products, we looked for TP53 mutations in DNA of patients with AT. We did not find any mutation in 6 patients, suggesting that TP53 mutations are not directly involved in the cancer susceptibility observed in AT.

PMID: 8500101 [PubMed - indexed for MEDLINE]